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Multisession Radiosurgery for Hearing Preservation

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Clinically relevant dose-tolerance limits with reliable estimates of risk in 1-5 fractions for cochlea are still unknown. Timmerman's limits from the October 2008 issue of Seminars in Radiation Oncology have served as the basis for clinical practice, augmented by updated constraints in TG-101 and QUANTEC, but the corresponding estimates of risk have not yet been well-reported. A total of 37 acoustic neuroma CyberKnife cases from Medstar Georgetown University Hospital treated in 3 or 5 fractions were combined with single-fraction Gamma Knife data from the 69 cases in Timmer 2009 to form an aggregate dataset of 106 cochlea cases treated in 1-5 fractions. Probit dose-response modeling was performed in the DVH Evaluator software to estimate normal tissue complication probability. QUANTEC recommends keeping single-fraction maximum dose to the cochlea less than 14 Gy to maintain less than 25% risk of serviceable hearing loss, and our 17.9% risk estimate for 14 Gy in 1 fraction is within their predicted range. In 5 fractions, our estimate of the Timmerman 27.5 Gy maximum cochlea dose limit was 17.4%. For cases in which lower risk is required, the Timmerman 12 Gy in 1 fraction and the TG-101 limit of 25 Gy in 5 fractions had an estimated risk level of 11.8% and 13.8%, respectively. High-risk and low-risk dose tolerance with risk estimates in 1-5 fractions are all presented.

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Radiosurgery or hypofractionated radiotherapy (stereotactic body radiotherapy [SBRT]) is a well-established modality for the management of acoustic neuromas (AN) that are slow-growing benign tumors. These tumors arise from the cochlea-vestibular nerve complex within the internal auditory canal and can expand into the cerebellopontine angle. A "wait-and-see" approach is an option but these tumors can grow causing compression of the seventh and eighth cranial nerves and brainstem, as well as hearing loss, and many patients inevitably require treatment.[1-4] Régis et al[3] found that only 78%, 43%, and 14% of patients in the wait-and-see group maintained tumor control and functional hearing at 1, 2, and 5 years, respectively, whereas the Gamma Knife group had 88%, 79%, and 60% of patients for the same endpoints and time periods. Although AN usually grow slowly, Kondziolka et al[4] observed that more than 95% of their patients in the "wait-and-scan" group had measurable growth by the 10-year follow-up. Common treatments of these tumors are microsurgical resection, radiation therapy, or conservative management with radiologic surveillance.[5,6] Potential complications following SBRT for AN include trigeminal neuropathy, facial nerve dysfunction, ataxia, and hearing loss.

Leksell[7] and Norén et al[8] were the first to treat AN with Gamma Knife (Elekta Inc, Stockholm, Sweden) beginning in the 1960s, with reports of very favorable results.[7-9] In the mid-1980s, with the worldwide availability of the Gamma Knife and with the development of linear accelerators adapted for

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stereotactic irradiation, this noninvasive radiation treatment became more popular. By the year 2000, several authors had claimed excellent local control rates with radiosurgery, comparable with surgery, but with a high rate of preservation of hearing and facial and trigeminal nerve function.[9-12] Seeking a potential fractionation benefit, several groups began fractionated regimens on a stereotactic linac[9,13-15] or CyberKnife (Accuray Inc, Palo Alto, CA).[16-19] However, despite more than 40 years of clinical use and numerous publications, quantitative estimates of complication risks as a function of cochlea dose remain elusive.

As SBRT is increasingly being applied for the treatment of AN, it is important to determine reliable dose-tolerance limits for the cochlea to guide clinical practice. The goal of this study was to determine clinically relevant SBRT dose-tolerance limits for hearing preservation, when treatments are given in 1-5 fractions, based on statistical analysis of clinical outcomes data.

Table 1 Summary of Patient and Treatment Characteristics

Characteristic	Present Study	Timmer et al[20]
Number of cases	37	69
Median age, y	58 (31-85)	53 (24-76)
Median follow-up, mo	51 (15-108)	14.2 (3-56)
Median tumor volume, cc	1.03 (0.14-7.60)	2.28 (0.02-10.20)
Number of cases per fraction		
1 Fraction	0	69
3 Fractions	2	0
5 Fractions	35	0
Delivery method	CyberKnife	Gamma Knife
<50 dB hearing preservation	4	6

Single-Fraction Cochlea Dose Tolerance

A PubMed search for cochlea AND ((stereotactic AND radiation) OR radiosurgery) found 96 articles in June 2015, but among them we found no dose-response models, and could only find a single publication with cochlea doses and hearing preservation outcomes for each patient, Timmer et al[20]. The cochlea D_{max} data from this Gamma Knife series of 69 patients treated from June 2003-November 2007 at the Radboud University Nijmegen Medical Center in The Netherlands are reproduced in Figure 1(A). Patient and treatment characteristics are already described,[20] so only the details most important for interpreting our dose-response model are summarized in Table 1. The Gardner-Robertson scale,[21] shown in Table 2, includes 3 frequency pure tone average (PTA) as well as speech discrimination scores. The Timmer et al[20] study did measure speech discrimination scores for each patient but unfortunately they were not published as a function of dose for each patient like the PTA was in Figure 1(A), so our probit dose-response model could only be based on PTA alone. The selected end point was 50 dB of hearing loss in 1 ear, which is part of the Gardner-Robertson scale for serviceable hearing.

Statistical modeling

The probit model[22,23] was used to estimate the normal tissue complication probability (NTCP) dose-response for cochlea D_{max} in terms of the normalized slope m and the $TD_{50}(V)$ 50% tolerance dose (TD) for a given partial volume (V) by

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2} dx \qquad (1)$$

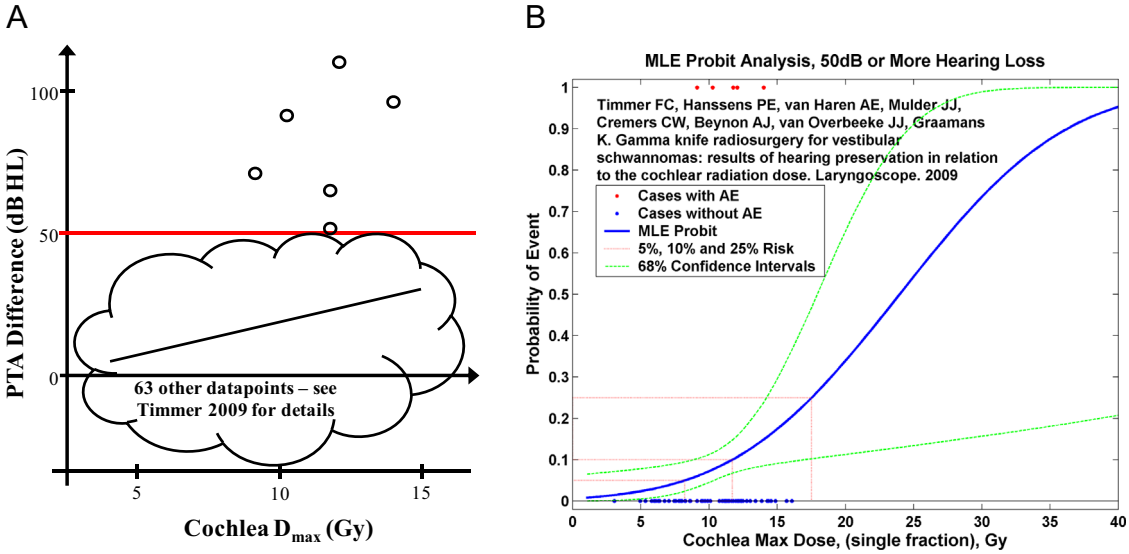


Figure 1 Single-fraction cochlea tolerance. (A) Change in pure tone average (PTA) from study by Timmer et al as a function of cochlea D_{max}; the 6 data points shown are the ones exceeding 50 dB of hearing loss and the rest may be found in the article by Timmer et al.[20] (B) Corresponding dose-tolerance model for the end point of 50 dB hearing loss. AE, adverse event; dB, decibel; MLE, maximum likelihood estimate. (Color version of figure is available online.)

Table 2 Gardner-Robertson Scale[21]

Grade	Description	PTA, dB	Speech Discrimination, %
I	Good-excellent	0-30	70-100
II	Serviceable	31-50	50-69
III	Nonserviceable	51-90	5-49
IV	Poor	91-max	1-4
V	None	Not testable	0

where $t=(Dv-TD_{50}(V))/(m \times TD_{50}(V))$, m is the normalized slope, and Dv is the dose to the given volume V. To determine statistical dose-tolerance limits from the cochlea data, we used the maximum likelihood parameter fitting technique[24,25] because of its effectiveness in extracting the most information from limited datasets. Maximum likelihood principles were derived by Fisher[26] and have been proven in many instances to be theoretically optimal. The maximum likelihood parameter fitting technique has been applied to NTCP modeling[24,25] by

$$L(\gamma_1,\gamma_2,\cdots)=\prod_{m_{\text{complications}}} NTCP_m(\gamma_1,\gamma_2,\cdots) \times \prod_{n_{\text{no complications}}} (1-NTCP_n(\gamma_1,\gamma_2,\cdots)) \quad (2)$$

For the model in Eq. (1), only 2 parameters need to be solved, $\gamma_1=m$ and $\gamma_2=\mathrm{TD}_{50}(V)$. This analysis was performed using the DVH Evaluator software tool (DiversiLabs LLC, Huntingdon Valley, PA). Confidence bands were estimated using the profile likelihood method.[27,28] The result is plotted in Figure 1(B) and summarized in Table 3.

Multisession Cochlea Dose Tolerance

Patient characteristics and details of the treatments have already been described[19] and are only briefly overviewed here. A total of 55 patients with vestibular schwannoma treated with CyberKnife at Georgetown University Hospital were assessed. All data were reviewed under an institutional review board approved retrospective protocol. A minimum of 12-month follow-up was required to be included in the analysis. Overall, 18 patients had either no ($n=9$) or $\leq$1-year ($n=9$) follow-up data; 37 patients with $\geq$1-year follow-up data were analyzed. Pre- and posttreatment radiographic digital imaging was only available on 32 patients. In all, 19 patients had pre- and postaudiogram data for analyses, 14 of whom had serviceable hearing before the radiation treatment. Hearing, facial nerve function, and tumor volume or mass effect were analyzed with the Gardner and Robertson,[21] House and Brackmann,[29] and Koos et al[30] scales, respectively. A total of 29 patients were reached by phone and perception of hearing preservation, as well as overall satisfaction with the treatment was evaluated.

Patient characteristics are summarized in Table 1. The median age was 58 years (range: 31-85) with a 70% male majority. The laterality was divided almost equally between left and right side. None of the patients had received any prior treatment for their tumor. Most patients (81%) presented with hearing loss as an initial symptom, whereas ataxia or disequilibrium and tinnitus were the presenting symptoms in 57% and 46% of the patients, respectively. None of the patients had any symptoms of the facial nerve involvement on presentation.

Treatment characteristics are also included in Table 1. The median tumor volume was 1.03 cc with a range from 0.14-7.60 cc. Most patients (95%) were treated with 25 Gy in 5 sessions, whereas only 2 patients were treated to 21 Gy in 3 fractions. Most tumors (54%) were Koos Grade 2.

Probit dose-response models of the 5-fraction data and the aggregate data were generated using the DVH Evaluator software, with the same end point and methodology as was used for the single-fraction dataset. Figure 1(B) is in terms of pure physical dose for the single-fraction dataset, and Figure 2 (A) is in terms of physical dose for the 5-fraction dataset. When each dataset was analyzed individually, no biological effective dose conversions were used, other than converting the two 3-fraction cases to 5-fraction equivalent dose.

A 3-fraction regimen using linear quadratic (LQ) conversion was chosen for the aggregate analysis to alleviate the uncertainty of the α/β parameter, as 3 fractions are midway between the fractionation of the 2 datasets. QUANTEC[31] used $\alpha/\beta=3$ Gy, and we iteratively determined that the α/β parameter with maximally likelihood fit was 4.2 Gy. However, the maximal effect of $\alpha/\beta=4.2$ Gy when converting any of the single-fraction or 5-fraction published dose-tolerance limits to 3-fraction equivalent doses was less than 3%, so we used $\alpha/\beta=3$ Gy for the remainder of the analysis. The Timmerman[32] limit of $D_{\max}=12$ Gy in 1 fraction had the largest difference; if $\alpha/\beta=4.2$ Gy, the LQ model equates this to 18.7 Gy in 3 fractions, but if $\alpha/\beta=3$ Gy, then it would be 19.2 Gy in 3 fractions, resulting in a difference of 2.7%. For the purpose of this initial dose-response study, we opted to use $\alpha/\beta=3$ Gy and the LQ model for data conversion. The 3-fraction aggregate model is shown in Figure 2(B), and this model was used to estimate all the risk levels of the published dose-tolerance limits in the DVH Risk Map[33] in Figure 3.

Discussion

Hearing loss following AN radiotherapy is a critical quality of life issue and the principle dose-limiting toxicity. Currently,

Table 3 Probit Dose-Response Model Results

Dataset	Fractions	Number of Cases	TD_{50}, Gy (68% CI)	m (68% CI)	LL_{max}
Timmer et al[20]	1 fx	69	23.98 (17.97-82.60)	0.3994 (0.28-0.65)	−19.63
Present study	5 fx	37	37.64 (30.77-65.12)	0.3251 (0.22-0.53)	−11.76
Aggregate	3 fx Equiv.	106	34.55 (28.71-53.43)	0.3764 (0.29-0.52)	−31.53

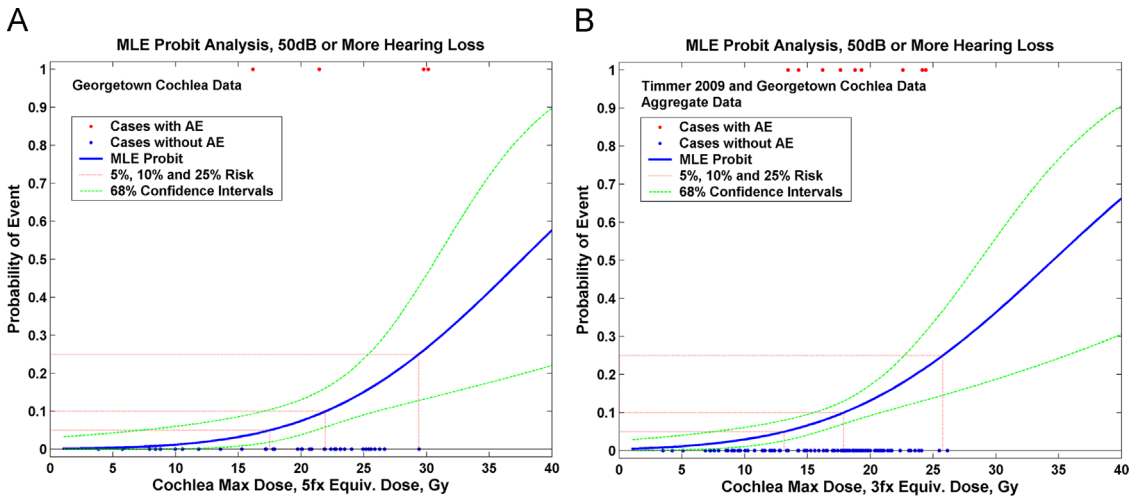


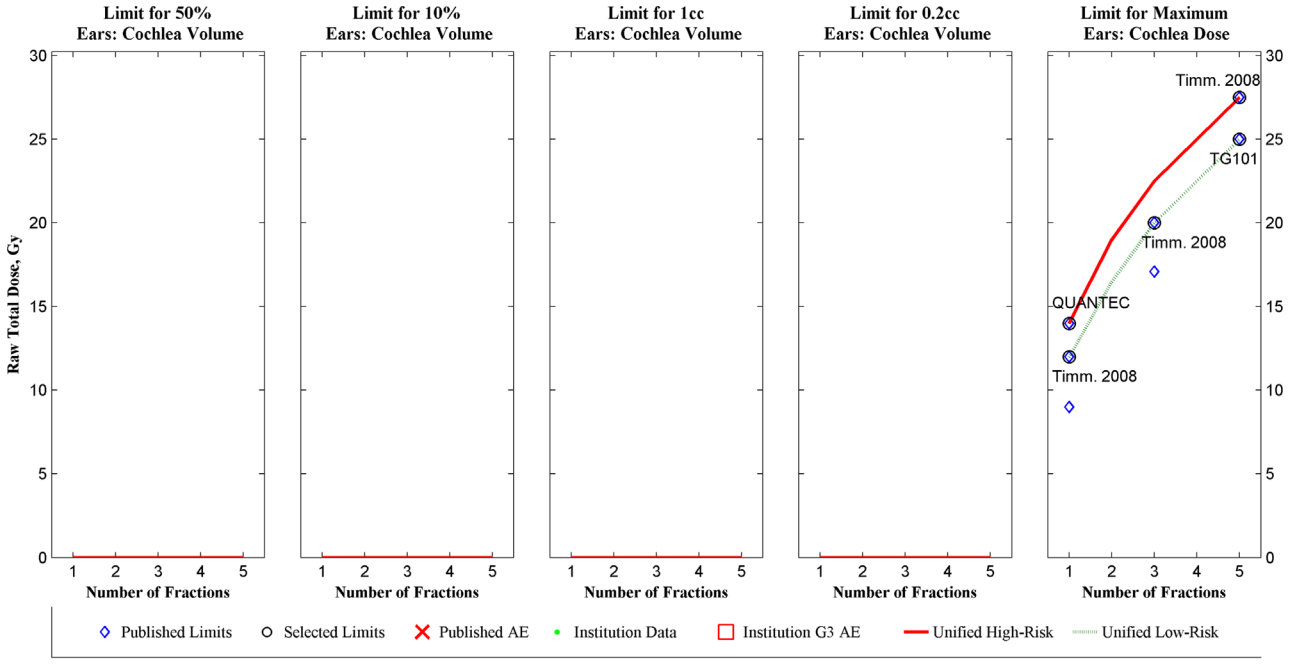
Figure 2 Dose-tolerance model for the end point of 50 dB hearing loss (A) for the 5-fraction patients in the present study in terms of physical dose, and (B) aggregate model of Timmer et al[20] single-fraction data with our 5-fraction data, modeled together in terms of 3-fraction equivalent dose. 3fx, 3 fraction; 5fx, 5 fraction; AE, adverse event; dB, decibel; MLE, maximum likelihood estimate. (Color version of figure is available online.)

there are limited data on dosimetric predictors of hearing loss following radiosurgery for AN. A better understanding of the dose-response relationship would enable clinicians to provide more realistic expectations to patients as they weigh their treatment options. Hearing preservation rates in Table 2 of QUANTEC ranged from 22%-94%,[31] and crude rates of hearing preservation in the present study and in Timmer et al[20] study are 89% and 91%, respectively, so these are within the favorable range of results.

The present study has several identifiable limitations. The patient population was derived from a single-institution cohort that can limit the translation of our work to the general population. In our study, we analyzed only patients with 12 months or more of follow-up, and the median follow-up was 51 months, up to 108 months. The Timmer et al[20] study showed shorter follow-up, with some patients having only 3 months of follow-up, which might not have been long enough for some complications to materialize. The differences in ranges of tumor volumes and the irradiated volumes of cochlea between the 2 datasets may also be an important factor, but the individual dose-volume data for the tumor and cochlea were not available. For the most accurate comparisons, full hearing audiometry should be evaluated consistently for several hundred patients for a predetermined length of follow-up such as 5 years. These limitations make it difficult to directly compare the results by Timmer et al[20] to those of our own patient population, so instead we simply created an aggregate model in 1-5 fractions. Despite the limitations, we feel that the present study provides a useful initial aggregate model for hearing preservation in 1-5 fractions, to guide clinical practice as the more rigorous results are forthcoming.

Perhaps the largest difference between the present study and the study by Timmer et al[20] is pretreatment serviceable hearing. In our previous study, the crude rate of hearing preservation of all 37 patients with at least 12 months of follow-up was 89%, and of the 26 patients with serviceable hearing pretreatment, the rate was 73% at median 5-year follow-up via telephone survey. In the study by Timmer et al[20] the crude rate of hearing preservation of all 69 patients was 91% but only 32 of the patients had serviceable hearing pretreatment, and among those patients hearing preservation with Tokyo class[34] A, B, or C was only 41%. However, Timmer et al[20] did not specify which D_{max} doses corresponded to the patients with serviceable hearing pretreatment, and they did not provide Tokyo class data as a function of D_{max}, so we can only analyze the overall hearing preservation. Nevertheless, it is remarkable that the study by Timmer et al[20] is the only one we could find that presented doses and outcomes per patient, so we are very appreciative of the data they did provide.

Fractionation offers to minimize radiation-associated toxicity by allowing normal tissue repair between treatments. If the 73% hearing preservation at a 5-year median follow-up could be compared with 41% hearing preservation with no patients followed to 5 years, it would be encouraging for the fractionated approach, but there are too many differences to make any such claims. The telephone survey is a useful indicator of patient-reported outcomes, but cannot be compared directly to the Tokyo classification or audiograms or the Gardner-Robertson scale. A more reasonable comparison is that among 14 fractionated cases with serviceable hearing and with audiograms, the hearing preservation rate was 78% at a median follow-up of 18 months. This length of follow-up is more similar to the median 14.2 month follow-up shown by Timmer et al,[20] but differences still remain in terms of the grading scales and other factors we have mentioned. These findings are particularly important, given that hearing loss is one of the principal dose-limiting toxicities, and further investigation is urgently needed to resolve the remaining questions conclusively. QUANTEC made insightful comments regarding several of the grading scales and provided an extensive set of recommendations for improved follow-up metrics that could help to discern outcomes more clearly in future studies.[31]



	Low Risk Limits					High Risk Limits				
	D50% Limit (Gy)	D10% Limit (Gy)	D1cc Limit (Gy)	D0.2cc Limit (Gy)	Dmax Limit (Gy)	D50% Limit (Gy)	D10% Limit (Gy)	D1cc Limit (Gy)	D0.2cc Limit (Gy)	Dmax Limit (Gy)
1 fx	-	-	-	-	**12.0, 11.8%**	-	-	-	-	**14.0, 17.9%**
2 fx	-	-	-	-	*16.5, 12.4%*	-	-	-	-	*19.0, 17.9%*
3 fx	-	-	-	-	**20.0, 13.2%**	-	-	-	-	*22.5, 17.7%*
4 fx	-	-	-	-	*22.5, 13.2%*	-	-	-	-	*25.0, 17.2%*
5 fx	-	-	-	-	**25.0, 13.8%**	-	-	-	-	**27.5, 17.4%**

Next

Figure 3 DVH Risk Map for cochlea in 1-5 fractions. (Color version of figure is available online.)

Stereotactic radiosurgery (SRS) in a single session is an accepted standard of care for the treatment of AN. A recent analysis of the patterns of care for ANs has shown an increase in the use of radiotherapy, particularly for patients with tumors under 2 cm in size.[35] However, the optimal radiotherapy approach (Gamma Knife SRS, fractionated stereotactic radiotherapy, single-fraction linear accelerator-based radiosurgery, and proton-based radiotherapy) remains unclear and there are no randomized studies comparing either surgery or radiotherapy, or a radiotherapeutic approach with another.

The size limitations for single-fraction SRS are generally recommended to be approximately 1.5-3 cm, with a known increase in side effects to normal tissue with increasing size.[36] The recommended dose in most institutions is $\leq$13 Gy. By allowing normal tissue repair between treatments, fractionated radiotherapy converts the radiobiological benefit of fractionation into a wider therapeutic window. In this study, we show low rates of hearing loss associated with fractionated radiotherapy. It can be difficult to compare results across the literature because of the differences in classifying progressive disease, as well as differing follow-up regimens and duration. Additionally, only smaller series are available with this concept of fractionated radiotherapy (RT) with no randomized clinical trials available. However, a recent meta-analysis of 449 patients that pooled data from 3 large German Centers showed comparable local control outcomes.[37] Similarly, at median follow-up of 67 months, loss of useful hearing was equivalent between the groups (16% for the SRS group and 14% for the fractionated RT group). These good control rates with fractionated radiation therapy deepen the controversy of the radiobiology of ANs. It also raises the question on whether size criteria should exist to guide clinicians in the application of single-fraction vs multisession fractionated RT.

The LQ model was originally developed for modeling of survival curves of cell lines[38-40] and eventually became the most widely used tool for describing time-dose relationships for conventional fractionation.[41-43] Intensive debate has arisen, however, regarding whether LQ is applicable at large doses per fraction or not,[44,45] and the debate continues to the present time.[46-54] Certainly, we could not resolve such a controversy with D_{max} doses of just a critical structure from only about a hundred cases. We took steps to mitigate the uncertainty, by first modeling the single-fraction data in pure physical dose by itself and also by modeling the 5-fraction data in physical dose by itself. Then by comparing these to a 3-fraction aggregate model, we could see that there were some differences, but none too alarming. The maximum likelihood fitted α/β was 4.2 Gy, and by comparing dose conversions with the $\alpha/\beta = 3$ Gy nominal value, differences in conversions of published dose-tolerance limits were all less than 3%. The largest percentage difference was for the Timmerman 2008 $D_{max} < 12$ Gy in 1-fraction limit, which equated to 18.7 Gy or 19.2 Gy in 3 fractions depending on whether $\alpha/\beta = 4.2$ Gy or $\alpha/\beta = 3$ Gy was used, respectively. Note that Timmerman 2008 used

20 Gy for the 3-fraction limit,[32] based on biological effective dose conversions using the universal survival curve,[55,32] and that is only about 4% different than 19.2 Gy. It is possible that alternate models such as universal survival curve, linear quadratic cubic,[56] or others,[57-59] may fit better, but it would require a large amount of data for testing. In the meantime, we have provided a probit model of cochlea dose tolerance in 1-5 fractions with LQ conversions, which should help clinical practice until these issues are more fully resolved. Future studies should also analyze the volume effects.

Conclusions

Emami et al[60] specified conventionally fractionated dose-tolerance limits for most grade 3 adverse events following radiotherapy in terms of TD 5/5 and TD 50/5 dose-tolerance limits—the 5% and 50% risk levels at 5 years. However, 50% risk of hearing loss is higher than desired—the QUANTEC guidance of 25% risk is more reasonable. Based on a dose-response model of 2 clinical datasets, the 14 Gy in 1-fraction limit and the 27.5 Gy in 5-fraction limit had 17.9% and 17.4% risk, respectively. For cases in which a lower risk is required, the 12 Gy in 1-fraction limit and the 25 Gy in 5-fraction limit had 11.8% and 13.8% risk, respectively. Caveats include the limited amount of data as well as the wide variety of grading and follow-up. Data from more patients and longer follow-up is required to determine the true dose tolerance, but these findings support current clinical practice for SBRT.

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